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Crystal Fong

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application for:

H. Michael Shepard and Michael P. Groziak

Application Serial No. To be Assigned

Filing Date: February 12, 2001

For: **ENZYME CATALYZED THERAPEUTIC AGENTS**

Examiner: To be Assigned

Group Art Unit: To be Assigned

Attorney's Docket No. 126745-200402

PRELIMINARY AMENDMENT

Box Patent Application
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to the examination of the subject application on the merits, consideration and entry of the following amendments are respectfully requested.

I. AMENDMENTS

Please amend the subject application as follows:

In the specification:

Page 1, line 14, after "priority" insert the following: --under 35 U.S.C. § 120 to U.S. Serial No. 09/234,961, filed January 22, 1999, now U.S. Patent No. _____, issued _____, which in turn claims priority--.

In the Claims:

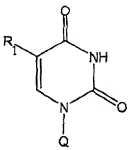
Please cancel claims 2 to 55, without prejudice or disclaimer.

Please add the following new claims:

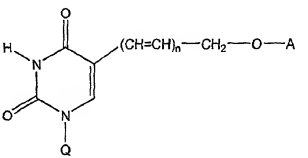
56. (New) A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with a phosphoryl or phorphoramidate prodrug that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme.

57. (New) A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a phosphoryl or phosphoramidate prodrug that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell.

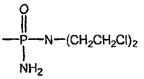
58. (New) A method for inhibiting the proliferation of a hyperproliferative cell comprising contacting the cell with an L- or D- isomer of the formula:



wherein R_1 is an electrophilic leaving group; or a compound of the formula:

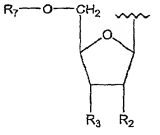


wherein n is an integer from 1 to 10; wherein A is a phosphoryl or phosphoramidyl moiety, or a substituent of the formula:



wherein Q is selected from the group consisting of a 5' substituted masked phosphoryl, a phosphoryl or phosphoramidyl moiety selected from the group consisting of a sugar substituent, a thio-sugar substituent, a carbasugar substituent, and a seco-sugar sustituent.

59. (New) The method of claim 58, wherein Q has the formula:



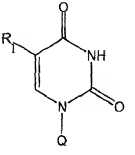
wherein R_7 is selected from the group consisting of masked phosphoryl moiety, phosphoramidyl moiety, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.

60. (New) The method of claim 58, wherein R_1 is a halogen.

61. (New) The method of claim 58, wherein R_1 is an alkenyl group of the formula $(\text{-}CH\text{=}CH)_n\text{-}R_4$, wherein n is an integer from 1 to 10, and R_4 is a substituent selected from the group consisting of H, a halogen, alkyl, alkene, alkyne, hydroxy, -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$, -NHCHO, a cyanide, cyanate, thiocyanate cyanide, thiocyanate halovinyl substituent, a halomercuric substituent, -

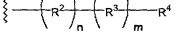
NHOH, -NHO-alkyl, and $NHNH_2$.

62. (New) A compound of the formula:



wherein:

R^1 is a substituent of the formula:



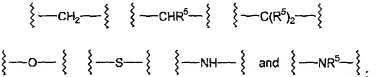
R^2 is a divalent moiety wherein n is from 1 to 10 and is selected from the group consisting of:

an unsaturated hydrocarbyl group;

an aromatic hydrocarbyl group consisting of one or more unsaturated hydrocarbyl groups; and,

a heteroaromatic group consisting of one or more unsaturated hydrocarbyl groups;

R^3 is selected from the group consisting of:



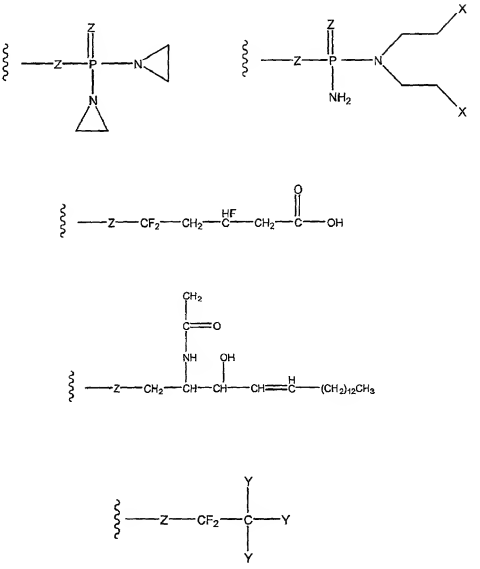
R^5 may be the same or different and is independently a linear or branched alkyl

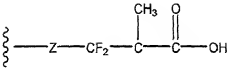
group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

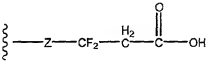
n is an integer from 1 to 10;

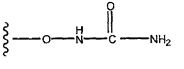
m is 0 or 1;

R^4 is a toxophore moiety selected from the group consisting of:







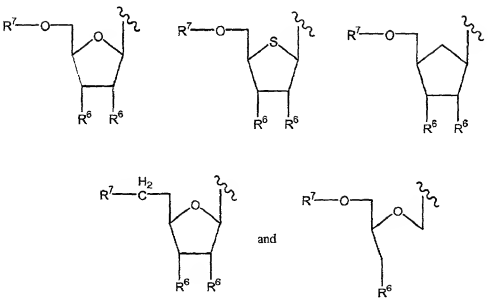


wherein X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

Y is independently -H or -F;

Z is independently -O- or -S-;

Q is selected from the group consisting of:



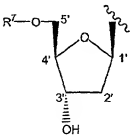
and

R^6 is independently -H, -OH, $-OC(=O)CH_3$, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl; and,

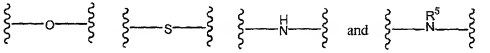
R^7 is hydrogen, a masked phosphate group, or a phosphoramidate group;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, consisting of a *D*-form, *L*-form, -anomeric form, and -anomeric form.

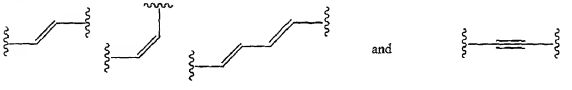
63. (New) A compound according to claim 62, wherein Q is:



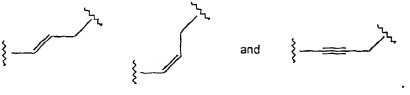
64. (New) A compound of claim 62, wherein R^3 is a divalent spacer moiety selected from the group consisting of:



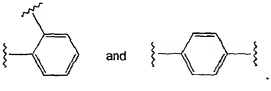
65. (New) A compound of claim 62, wherein R^2 is an unsaturated hydrocarbyl group selected from the group consisting of:



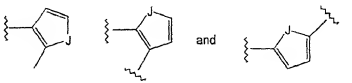
66. (New) A compound of claim 62, wherein R^2 and R^3, taken together form a structure selected from the group consisting of:



67. (New) A compound of claim 62, wherein R^2 is an aromatic hydrocarbyl group selected from the group consisting of:

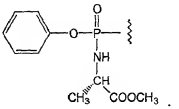


68. (New) A compound of claim 62, wherein R^2 is a heteroaromatic group selected from the group consisting of:

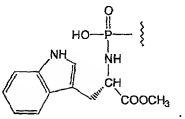


wherein J is -O-, -S-, -Se-, -NH-, or $-NR^{ALK}-$, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

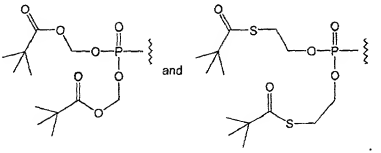
69. (New) A compound of claim 62, wherein R^7 is selected from the group consisting of:



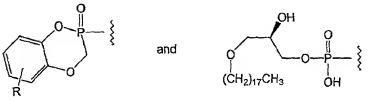
70. (New) A compound of claim 62, wherein R^7 is selected from the group consisting of:



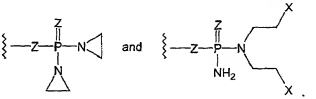
71. A compound of claim 62, wherein R^7 is selected from the group consisting of:



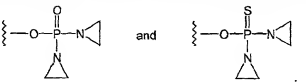
72. (New) A compound of claim 62, wherein R^7 is selected from the group consisting of:



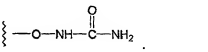
73. A compound of claim 62, wherein R^4 is selected from the group consisting of:



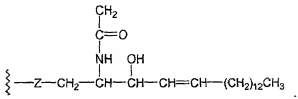
74. A compound of claim 62, wherein R^4 is selected from the group consisting of:



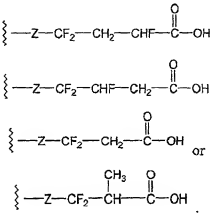
75. (New) A compound of claim 62, wherein R^4 is:



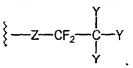
76. (New) A compound of claim 62, wherein R^4 is:



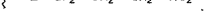
77. (New) A compound of claim 62, wherein R^4 is:



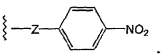
78. (New) A compound of claim 62, wherein R^4 is:



79. (New) A compound of claim 62, wherein R^4 is:



80. (New) A compound of claim 62, wherein R^4 is:



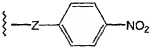
81. (New) A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with an effective amount of a compound of claim 62.

82. (New) The method of claim 81, wherein the hyperproliferative cell is characterized by the endogenous overexpression of an intracellular enzyme.

83. (New) The method of claim 82, wherein the enzyme is thymidylate synthase.

84. (New) A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a compound of claim 62.

85. (New) A method for screening for a therapeutic agent, comprising contacting a target cell with a compound of claim 62, wherein R^4 is:



86. (New) A method of inhibiting the proliferation of a pathological cell that contains an intracellular target enzyme, comprising:

(a) contacting the cell with a compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic by-product by means of the intracellular target enzyme.

87. (New) A method of inhibiting the proliferation of a hyperproliferative cell that contains enzymes that are over expressed and which contribute to drug resistance, comprising:

(a) contacting the cell with the compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic byproduct by means of the enzyme.

88. (New) The method of any of claims 86 or 87, wherein the hyperproliferative cell is a cancer cell.

89. (New) The method of claim 88, wherein the cancer cell is selected from the group consisting of a colorectal cell, a head and neck cancer cell, a breast cancer cell, a liver cancer cell and a gastric cancer cell.

II. REMARKS

Claims 2 to 55 are canceled without prejudice or disclaimer. Claims 56 to 89 are added. Accordingly, claims 1 and 56 to 89 are pending in the subject application. Support for the newly added claims is found in the original claims as filed, and in the specification which supports these claims. No new matter is added by these amendments and entry thereof is respectfully requested.

The subject application is a continuation of U.S. Serial No. 09/235,961, in which the Examiner indicated allowable subject matter. The non-allowed claims were canceled in that application without prejudice or disclaimer and are under continued examination herein.

If a telephone interview would advance prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant

Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0974**, referencing Attorney Docket No. 126745200402. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: February 12, 2001 By: Antoinette Konski

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Reg. No. 34,202

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